

AMENDMENTS TO THE SPECIFICATION

Please amend the specification as follows (deleted matter is indicated by brackets and added matter is indicated by underlining):

Please replace the paragraph that begins on page 2, line 11, with the following rewritten paragraph:

--Opioids repress the propagation of pain stimuli. Besides the immediate inhibition of neuronal excitatory signal transduction in the spinal cord caused by opioids, an activation of such nerve tracts is relevant, which project [form] from the brainstem into the spinal cord. This activation results in an inhibition of pain propagation in the spinal cord. Moreover, opioids limit the pain reception of the thalamus and by affecting the limbic system they influence the affective pain evaluation. --

Please replace the paragraph that begins on page 2, line 22, with the following rewritten paragraph:

-- Opioid analgesics are considered to be strong agonists if they bind with high affinity to opioid receptors and induce a strong inhibition of pain reception. Substances that also bind with high affinity to opioid receptors, but that do not provoke a reduction of pain reception and which thereby counteract the opioid agonists, are designated as antagonists. Depending on the binding behaviour and the induced activity, opioids can be classified as pure agonists, mixed agonists/antagonists and pure antagonists. Pure antagonists comprise, for example, naltrexone, naloxone, nalmefene, nalorphine, nalbuphine, naloxoneazinen, methylnaltrexone, ketylcyclazocine, norbinaltorphimine, naltrindol, 6-13-naloxol [und] and 6-13-naltrexol (Forth W.; Henschler, D.; Rummel W.; Starke, K.: Allgemeine und Spezielle Pharmakologie und Toxikologie, 7. Auflage, 1996, Spektrum Akademischer Verlag, Heidelberg Berlin Oxford).--

Please replace the paragraph that begins on page 3, line 7, with the following rewritten paragraph:

--Due to their good analgesic efficiency compounds such as oxycodone, tilidine, buprenorphine [und] and pentazocine, have been used in the form of medicaments for pain

therapy. Medicaments such as Oxigesic® (wherein oxycodone is the analgesic active compound) [und] and Valoron® (wherein tilidine is the analgesic active compound) have proven valuable for pain therapy. --

Please replace the paragraph that begins on page 4, line 17, with the following rewritten paragraph:

--U.S. Pat. Nos. 3,773,955 [und] and 3,966,940 suggested to formulate analgesics in combination with naloxone, in order to prevent dependence-promoting effects such as euphoria and the like, upon parenteral application. The avoidance of side effects such as obstipation has not been addressed. --

Please replace the paragraph that begins on page 12, line 1, with the following rewritten paragraph:

-- The independent release feature preferably refers to the situation where preparations of substantially equal composition are compared for the release profile. Preparations of substantially equal composition have different amounts of the active compounds but are otherwise basically the same with respect to the components of the composition which essentially influence the release behaviour. --

Please replace the paragraph that begins on page 12, line 7, with the following rewritten paragraph:

-- If e. g. the above-mentioned preparations are compared (with the first preparation comprising 12 mg oxycodone and 4 mg naloxone and the second preparation comprising 12 mg oxycodone and 6 mg naloxone) both preparations, provided that they have the same total weight, will provide for the same release profile for oxycodone and naloxone if the difference in the naloxone amount is replaced by a component in the formulation that typically does not influence the release behaviour. As shown in the Example section, the difference in the amount of naloxone [my] may be replaced by a typical pharmaceutically inert filler such as lactose without changing the release profiles. --

Please replace the paragraph that begins on page 16, line 1, with the following rewritten paragraph:

--Even though this might not be expressly stated, the term "agonist" or "antagonist" always comprises pharmaceutical acceptable and equally acting derivatives, salts and the like. If, for example, oxycodone or naloxone is mentioned, this also comprises, besides the free base, their hydrochloride, sulfate, bisulfate, tetrates, nitrates, citrates, bitrates, phosphates, malates, maleates, hydrobromides, [hydrojodide] hydroiodide, fumarates, succinates and the like.--

Please replace the paragraph that begins on page 19, line 1, with the following rewritten paragraph:

-- Matrices that are in accordance with the invention can be used to produce preparations that release active compounds in a sustained, independent and invariant manner and that release equal amounts of the active compounds per time unit. Specifically, this means that in the case of a oxycodone/naloxone combination containing 12 mg oxycodone [und] and 4 mg naloxone, 25% oxycodone and 25% naloxone are released within the first 4 hours. Correspondingly, in the case of a oxycodone/naloxone combination containing 24 mg oxycodone and 8 mg naloxone, 25% oxycodone and 25% naloxone are released during the first 4 hours, with the deviation in both cases being no more than 20% of the mean value (which in this case is 25% oxycodone or naloxone).--

Please replace the paragraph that begins on page 20, line 1, with the following rewritten paragraph:

--Yet another preferred embodiment of the invention relates to preparations that release between 40% to 80%, preferably between 45% to 75%, more preferably between 45% to 70% and even more preferably between 45% to 50%, 50% to 55%, 55% to 60%, 60% to 65% or 65% to 70% of oxycodone and/or naloxone after 2 hours. Preferred embodiments also comprise preparations that release approximately 45%, approximately 50%, approximately 55%, approximately 60%, [approximately 65%] approximately 65% or approximately 70% of oxycodone and/or naloxone after 2 hours--

Please replace the paragraph that begins on page 21, line 9, with the following rewritten paragraph:

--Lactose, glucose or saccharose, starches and their hydrolysates, microcrystalline cellulose, [cellatose] cellactose, sugar alcohols such as sorbitol or mannitol, polysoluble

calcium salts like calciumhydrogenphosphate, dicalcium-or tricalciumphosphat may be used as fillers. --

Please replace the paragraph that begins on page 22, line 16 with the following rewritten paragraph:

--Preparations in accordance with the invention can be produced as all common application forms which, on principle, are suitable for retardation formulations and which ensure that the active compounds are released in a manner in accordance with the invention. Especially suitable are tablets, multi-layer tablets and capsules. Additional application forms like granules or powders can be used, with only those [applications] application forms being admissible that provide a sufficient retardation and a release behaviour in accordance with the invention. --

Please replace the paragraph that begins on page 24, line 23, with the following rewritten paragraph:

--Generally, the temperatures of the heating zones have to be selected such that no temperatures develop that may destroy the pharmaceutically active compounds. The feeding rate [und] and screw speed will be selected such that the pharmaceutically active compounds are released from the preparations produced by extrusion in a sustained, independent and invariant manner and are storage stable in the matrix. If e.g. the feeding rate is increased, the screw speed may have to be increased correspondingly to ensure the same retardation. --

Please replace the table that begins on page 28, line 12, with the following rewritten table:

Preparation (designation)	Oxy/Nal-Extr
[oxycodone] <u>Oxycodone</u> HCl	20 mg
[naloxone] <u>Naloxone</u> HCl	10 mg
Kollidon 30	6 mg
Lactose Flow Lac 100	49.25 mg
Ethylcellulose 45 cpi	10 mg
Stearyl alcohol	24 mg
Talcum	2.5 mg
Mg-Stearate	[1,25 mg] <u>1.25 mg</u>

Please replace the paragraph that begins on page 30, line 1, with the following rewritten paragraph:

--The release values refer to oxycodone or naloxone (line 2) and are given as percentages. The mean value for the release of naloxone at e. g. 420 min is [92,7%] 92.7%. The maximal deviation at 420 min is 1%. Oxy and Nal stand for oxycodone and naloxone and indicate the active compound which has been measured. --

Please replace the table that begins on page 30, line 14, with the following rewritten table:

Time (min)	Oxy/Nal-Extr-[1,2-O] <u>1.2-O</u>	Oxy/Nal-Extr-[1,2-N] <u>1.2-N</u>
	Oxy	Nal
0	0	0
15	24.1	24.0
120	62.9	63.5
420	92.9	93.9
720	96.9	98.1

Please replace the table that begins on page 31, line 4, with the following rewritten table:

Time (min)	Oxy/Nal-Extr-[6,5-O] <u>6.5-O</u>	Oxy/Nal-Extr-[6,5-N] <u>6.5-N</u>
	Oxy	Nal
0	0	0
60	48.1	49.2
120	65.0	64.7
240	83.3	81.8
420	94.1	92.3

Please replace the paragraph that begins on page 33, line 1, with the following rewritten paragraph:

-- The release values refer to tilidine or naloxone (line 2) and are given as percentages. The mean value for the release of naloxone at e.g. 420 min is [78,87%] 78.87%. The maximal deviation at 420 min is [20,4%] 20.4%. Til [und] and Nal stand for tilidine and naloxone and indicate the active compound tested. --

Please replace the paragraph that begins on page 36, line 1, with the following rewritten paragraph:

--One recognizes from the values listed in the Table that in the case of a non-swellable diffusion matrix based on ethylcellulose, the release rates of different naloxone amounts, independent of the [oxycodone] oxycodone amount, remain substantially equal.--

Please replace the table that begins on page 37, line 1, with the following rewritten table:

Preparation (designation)	OxN20/1- Extr-D	OxN20/1- Extr-E	OxN20/10- Extr-B	OxN20/10- Extr-C	OxN20/10- Extr-D	OxN20/10- Extr-E
[oxycodone HCl] <u>Oxycodone HCl</u>	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg
[naloxoneHCl] <u>NaloxoneHCl</u>	1 mg	1 mg	10 mg	10 mg	10 mg	10 mg
Lactose Flow Lac100	56.25 mg	56.25 mg	54.25 mg	65.25 mg	60.25 mg	55.25 <u>mg</u>
Kollidon® 30	7 mg	6 mg	6 mg	7.25 mg	7.25 mg	7.25 mg
Ethylcellulose	11 mg	12 mg	10 mg	12 mg	12 mg	12 mg
Stearyl alcohol	24 mg	24 mg	24 mg	28.75 mg	28.75 mg	28.75 mg
Talcum	1.25 mg	1.25 mg	1.25 mg	1.25 mg	1.25 mg	1.25 mg
Mg-Stearate	2.5 mg	2.5 mg	2.5 mg	2.5 mg	2.5 mg	2.5 mg